Leukemia insights

OCTOBER 2019

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, MD, and Marina Konopleva, PhD, MD, and sponsored in part by the Charif Souki Cancer Research Fund, we discuss novel therapies and approaches in blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Focus on Rare Blood Cancers: Novel Approaches in Blastic Plasmacytoid Dendritic Cell Neoplasm

In December 2018, the Food and Drug Administration (FDA) approved tagraxofusp (formerly DT-IL3, SL-401, Stemline), the first and only targeted agent for patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) (Economides/Pemmaraju N et al Expert Rev Clin Pharmacol. 2019 Oct 1:1-6). This was also the first approval for a CD123-targeted agent in oncology. This approval was largely based on the pivotal Phase I/II multi-center clinical trial, which included frontline and relapsed/refractory patients with BPDCN (Pemmaraju et al N Engl J Med. 2019 Apr 25; 380(17):1628-1637). Tagraxofusp was given as a single agent, and the median age of patients was 70 years (range 22-84 years). Among 29 patients treated in the frontline setting, overall response rate was 90%, with 72% of frontline patients achieving complete remission. Forty-five percent of these patients received therapy as a bridge to stem cell transplant. In the relapsed/refractory (R/R) setting, a 67% overall response rate was observed. Despite these promising results, response duration can be short, thus more therapies and combination approaches are urgently needed.

Our BPDCN Clinic and BPDCN Research Program have several clinical trials and novel approaches to build on the initial progress seen in our field, and to improve outcomes for patients with BPDCN.

1. Tagraxofusp (SL-401) and H-CVAD and Venetoclax

This Phase II trial that combines tagraxofusp with venetoclax and H-CVAD aims to build on the results of the single-agent tagraxofusp experience in newly diagnosed patients with BPDCN. The regimen combines the three most active therapies, previously given individually, including CD123 targeted, BCL-2 targeted, and intensive chemotherapy in one comprehensive strategy. The study will open initially only at MD Anderson as our new frontline strategy, and will investigate the safety and efficacy of this combination.

2. Venetoclax for Relapsed/Refractory BPDCN

This Phase I study of venetoclax for patients with BPDCN (NCT03485547) is based on our groups' pre-clinical and clinical work investigating the role of BCL-2 inhibition in BPDCN

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(Montero et al Cancer Discov. 2017 Feb;7(2):156-164; DiNardo et al Am J Hematol. 2018 Mar;93(3):401-407; Pemmaraju N, Konopleva M, Lane AA, N Engl J Med. 2019 Feb 14;380(7):695-6). It is done in partnership with colleagues at Dana-Farber Cancer Center and is specifically dedicated to patients with R/R disease. Venetoclax is already FDA approved for patients with CLL, and, more recently, for older patients with AML (in combination with low-dose cytarabine or hypomethylating agents (Konopleva et al Cancer Discov. 2016 Oct; 6(10):1106-1117).

3. IMGN632 in Relapsed/Refractory CD123+ Malignancies

This Phase I trial of IMGN632 (NCT03386513), a conjugated CD123-targeted agent consisting of a novel DNA-alkylating payload, aims to investigate its use in R/R hematologic malignancies including BPDCN, acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) (Economides, Konopleva, Pemmaraju Ther Adv Hematol. 2019 Sep 23). IMGN632 was shown to have activity and prolong survival in AML xenograft models (Adams et al Blood 2016: abstract 2832). Patients with AML and BPDCN have been enrolled, and preliminary results presented at the 2018 American Society of Hematology meeting established safety and showed an early signal for efficacy (Daver et al ASH 2018). We hope to have more results later this year.

4. MB-102 in Relapsed/Refractory BPDCN

This Phase I/II multicenter trial (NCT04109482) will assess the safety and efficacy of MB-102 in Patients with R/R BPDCN, AML, and high-risk myelodysplastic syndrome (MDS). It features a novel, autologous chimeric antigen receptor T-cell (CAR-T) construct targeted against CD123. It will begin as a Phase I dose-escalation study for patients with R/R BPDCN.

5. Stem Cell Transplant and Post-SCT Maintenance in BPDCN

Understanding and optimizing the role of stem cell transplant (SCT) in patients with BPDCN is an emerging area of research. At the 2019 European Hematology Association meeting, we reported on outcomes among 24 patient with BPDCN who underwent SCT (n=14 allogeneic, n=10 autologous) with median age of 52 years (range 18-79). Two-year overall survival (OS) was 26% (4% allo, 57% auto) and 56% (24% allo, 80% auto) in auto and allo-SCT, respectively (p=0.33). In patients transplanted before or after 2015, 2-year progression free survival (PFS) was 13% vs. 54% (p=0.009), respectively, and 2- year OS was 13% and 68% (p=0.017). (Qazilbash/Pemmaraju et al EHA 2019). We are working with our SCT colleagues at MD Anderson to open post-SCT maintenance trials for patients with BPDCN.

6. Tagraxofusp (SL-401) in BPDCN and Beyond

Now that the original SL-401 monotherapy trial for patients with BPDCN is closed to new patient entry, we continue to follow patients for long-term survival (Pemmaraju et al ASH 2018). Currently, we use tagraxofusp as standard of care for patients not eligible for clinical trials and treat patients on the Leukemia inpatient service, with close monitoring of daily weight, creatinine, liver function tests and albumin. It is crucial to monitor these parameters carefully as the most significant toxicity is capillary leak syndrome (CLS), which can be fatal and led to an FDA-mandated "black box" warning. (Pemmaraju N Clin Adv Hematol Oncol. 2019 Apr; 17(4):207-209). Also, tagraxofusp continues to be investigated in several clinical trials all available at MD Anderson, including for patients with: AML (Togami/Lane et al JCI 2019 Oct 14. pii: 128571. doi: 10.1172/JCI128571. [Epub ahead of print]) (tagraxofusp + azacitidine + venetoclax in patients with AML; NCT03113643); high-risk MDS (tagraxofusp + azacitidine ; NCT03113643); CMML (tagraxofusp monotherapy; NCT02268253; Patnaik et al ASCO 2019 and EHA 2019); and in myelofibrosis (tagraxofusp monotherapy; NCT02268253; Pemmaraju et al ASCO 2019, EHA 2019).

7. Importance of Pathology and Molecular Markers in BPDCN

Specialized pathology review – both dermatopathology and hematopathology -- is essential in the diagnosis of BPDCN. Traditionally, we have noted flow cytometry/immunohistochemistry markers that form the backbone of a diagnosis are CD123, CD4 and CD56 (think "CD123456") (Alayed Am J Hematol. 2013 Dec; 88(12):1055-61) (Pemmaraju and Konopleva, The Hematologist 2018) in combination with additional markers that add specificity: TCL-1 and CD303. There are exceptions, however, as in rare cases that are CD56 negative. The identification of TCF4 with CD123 as a novel dual marker has added further specificity to make the diagnosis (Sukswai/Khoury J Am J Surg Pathol. 2019 Oct; 43(10):1429-1437). Future directions include investigating and understanding other important markers, such as PD-1 and PDL-1 (Aung PP/Khoury J Cancers [Basel]. 2019 May 19; 11(5).

For more information or patient referral for BPDCN, please contact Drs. Naveen Pemmaraju or Marina Konopleva. Follow Dr. Pemmaraju on Twitter @doctorpemm and at #BPDCN for the latest updates.

Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress.

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